Open Access Epidemiology and Prevention

Journal of Renal Endocrinology

J Ren Endocrinol 2023;9:e25084.
https://www.jrenendo.com
doi: 10.34172/jre.2023.25084

Nickan Research Institute

Sodium-glucose co-transporter-2 inhibitors in renal failure patients; expanding indications and prospective trends

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Implication for health policy/practice/research/medical education:
Following a diminution in renal function, the quantity of glucose released into the renal proximal tubular lumen will consequently decrease; therefore, the anti-hyperglycemic effect of sodium-glucose co-transporter-2inhibitors will be diminished.

Keywords: Sodium-glucose co-transporter-2 inhibitors, Renal failure, Type-2 diabetes mellitus, Chronic renal failure

Citation: Nasri H, Ghanbari-nejad S, Dehghani M, Dieti A. Sodium-glucose co-transporter-2 inhibitors in renal failure patients; expanding indications and prospective trends. J Ren Endocrinol. 2023;9:e25084. doi: 10.34172/jre.2023.25084.

Sodium-glucose co-transporter-2 inhibitors (SGLT2i) are glucose-reducing compounds, that exert their effect by higher affinity reversible competitive binding to sodium-glucose co-transporter-2 (SGLT2), located in the first two segments of the proximal convoluted tubules of nephrons in the kidney, where most glucose reabsorption occurs. This prevents reabsorption in this section of the nephron, leading to the removal of excess glucose from the body and blood glucose regulation, via glucosuria (1). The lowering glucose effect of SGLT2i is independent of the action of insulin. However, these seem to have an indirect diminishing effect on pancreatic beta-cell proliferation and apoptosis levels and have been also described to reduce the levels of glycated hemoglobin (HbA1c) in the blood of individuals with type-2 diabetes (T2D), thus reducing even more the amount of required insulin in these patients (1,2). The sodium-glucose co-transporter-1 (SGLT1) is located in the luminal membrane of cells lining the third section of the proximal tubules, where reabsorption of the remaineder low-concentrations of glucose occurs. SGLT1 is also found abundant on the apical membrane of enterocytes, where it facilitates glucose reabsorption from the intestinal lumen (3).

The fact that the effect of SGLT2i is initiated shortly after their administration, signifies a mechanism beyond that of glycemic control (4). In their review, Yau et al report that glucosuria in individuals with T2D as well as non-diabetic subjects, may reach levels beyond 100 g and 60 g of glucose, respectively, following administration with SGLT2i. However, the HbA1c, systolic blood pressure and weight-lowering efficacy of these agents appeared to be reduced in type-II diabetic patients with impaired kidney function (4). Several studies show that the use of SGLT2i prevents the progression of chronic kidney failure and provides a therapeutic key approach in managing diabetic and non-diabetic patients with IgA nephropathy, focal segmental glomerulosclerosis, and heart failure (4), and reducing the risk of hospitalization (5).

Skrabic et al discuss the pathological target points by which SGLT2i appear to be beneficial to chronic kidney disease (CKD), with reference to clinical evidence obtained from studies involving patients with diabetic kidney disease and diabetes melitus, across different populations groups, highlighting their current effectiveness and safety (6). At the same time reference is also made to adverse effects, associating the use of SGLT2i with an increased risk of urinary tract infections, possibly due to the increased flow of glucose through the urinary tract (6,7), but also a risk of potential dehydration, hypotension, depletion in bone composition and a decline in renal function in those susceptible elderly patients with impaired renal function as well as those treated with diuretics (7). According to Alhwiesh ets al, the use of SGLT2i in dialysis patients is not associated with change of the peritoneal transport status, and additionally enhances diabetic control and improves ultra-filtration volume, average urine volumes and decreased most of the inflammatory markers the serum and effluent of automated-peritoneal dialysis patients with T2D (8). The authors state that SGLT2i, even though they do not affect the urine creatinine clearance, their use may lead to some hypouricemic effect in such patients.

Received: 16 February 2023, Accepted: 17 April 2023, ePublished: 25 April 2023

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Li et al conducted a meta-analysis assessing the safety of SGLT2i on renal outcomes in patients with CKD. Across the spectrum of different estimated glomerular filtration rates (eGFR > 30 mL/min/1.73 m^2), the administration of SGLT2i was associated with significant renal benefits (9). This result was consistent with those from previous meta-studies confirming the renal benefits of SGLT2i in patients with low eGFR (5).

In summary, SGLT2i, as a new type of antidiabetic agent, has a moderate blood glucose regulatory effect.

The underlying mechanism of reno-protection is blocking the sodium uptake in proximal tubule, leading to increased sodium concentration in the distal convoluted tubule, provoking the sodium signal to macula densa, directing to afferent arteriolar contraction and decreased glomerular pressure, proteinuria and inflammation. However, these agents need to be further investigated for their nephroprotective impact in patients with chronic renal failure with different baseline features and underlying diseases. Nevertheless, SGLT2i provide a valuable therapeutic tool for the management of diabetic kidney disease and primary stages of chronic renal failure.

Authors' contribution

Conceptualization: HN.
Validation: HN.
Investigation: HN.
Resources: HN.
Data curation: HN.
Writing—original draft preparation: SGH-n, HN.
Writing—review and editing: AD, HN, MD, SGH-n.
Supervision: HN.
Project administration: HN.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Conflicts of interest

The authors declare that they have no competing interests.

Funding/Support

Nil.

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